EP04/6604

PCT/EP2004/006607

REC'D 15 JUL 2004

WIPO PCT

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed A N Brewer

Dated 10 May 2004

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

1/77

THE PATENT OFFICE
B
19 JUN 2003
LONDON

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

19 JUN 2003

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your Reference — SJB/PB60264P

20JUN03 E816522-1 D02955
P01/7700 0.00-0314369.0

2. Patent application number *(The Patent office will fill in this part)* — 0314369.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its corporation — GB

4735870003

4. Title of the invention — CHEMICAL COMPOUNDS

5. Name of your agent *(if you know one)* — SUZANNE BAKER

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY (CN9 25.1)
980 GREAT WEST ROAD
BRENTFORD
MIDDLESEX
TW8 9GS

Patents ADP number *(if you know it)*

8072555004

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

YES

See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Description	36
Claim(s)	2
Abstract	2
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature SUZANNE BAKER **19 June, 2003**
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

AMANDA WILKINSON
020 8047 4493

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication of communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the patent Act 1977 stops you from applying for a patent abroad without first getting written permission form the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been received

a) *Notes*

If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form*

If you have answered "Yes" Patents Form 7/77 will need to be filed.

d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

CHEMICAL COMPOUNDS

Field of the Invention

The present invention relates to a novel class of chemical compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine, particularly use in the amelioration of a clinical condition for which a Factor Xa inhibitor is indicated.

Background of the Invention

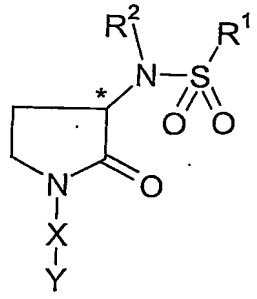
Factor Xa is a member of the trypsin-like serine protease class of enzymes. It is a key enzyme in the coagulation cascade. A one-to-one binding of Factors Xa and Va with calcium ions and phospholipid converts prothrombin into thrombin. Thrombin plays a central role in the mechanism of blood coagulation by converting the soluble plasma protein, fibrinogen, into insoluble fibrin. The insoluble fibrin matrix is required for the stabilisation of the primary hemostatic plug. Many significant disease states are related to abnormal hemostasis. With respect to the coronary arterial vasculature, abnormal thrombus formation due to the rupture of an established atherosclerotic plaque is the major cause of acute myocardial infarction and unstable angina. Both treatment of an occlusive coronary thrombus by thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA) are often accompanied by an acute thrombotic reclosure of the affected vessel which requires immediate resolution. With respect to the venous vasculature, a high percentage of patients undergoing major surgery in the lower extremities or the abdominal area suffer from thrombus formation in the venous vasculature which can result in reduced blood flow to the affected extremity and a pre-disposition to pulmonary embolism. Disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer and is characterised by the rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the vasculature leading to widespread organ failure. Beyond its direct role in the formation of fibrin rich blood clots, thrombin has been reported to have profound bioregulatory effects on a number of cellular components within the vasculature and blood, (Shuman, M.A., Ann. NY Acad. Sci., 405: 349 (1986)).

A Factor Xa inhibitor may be useful in the treatment of acute vascular diseases such as acute coronary syndromes (for example primary and secondary prevention of myocardial infarction and unstable angina and treatment of prothrombotic sequalae associated with myocardial infarction or heart failure), thromboembolism, acute vessel closure associated

with thrombolytic therapy and percutaneous transluminal coronary angioplasty, transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke. Factor Xa inhibitors may also be useful in preventing thrombosis and complications in patients genetically predisposed to arterial thrombosis or venous thrombosis and patients that have a disease-associated predisposition to thrombosis (e.g. type 2 diabetics). Thrombin has been reported to contribute to lung fibroblast proliferation, thus, Factor Xa inhibitors could be useful for the treatment of some pulmonary fibrotic diseases. Factor Xa inhibitors could also be useful in the treatment of tumour metastasis, by suppressing coagulation and thus preventing fibrin deposition and its concommittant facilitation of metastasis. A Factor Xa inhibitor may also have utility as an anti-inflammatory agent through its inhibition of FXa mediated activation of protease-activated receptors (PAR 1-4). A Factor Xa inhibitor may also have utility as an anti-atherosclerotic agent through the suppression of platelet-activation. Thrombin can induce neurite retraction and thus Factor Xa inhibitors may have potential in neurogenerative diseases such as Parkinson's and Alzheimer's disease. Factor Xa inhibitors may also have utility as anticoagulant agents in connection with the preparation, storage, fractionation or use of whole blood. They have also been reported for use in conjunction with thrombolytic agents, thus permitting the use of a lower dose of thrombolytic agent.

Description of the Invention

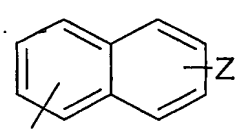
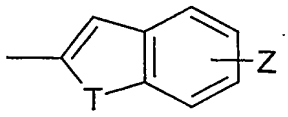
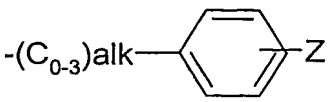
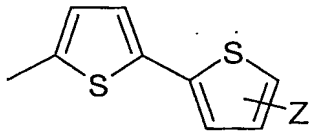
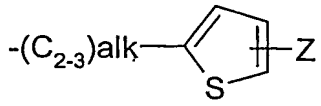
The present invention provides compounds of formula (I):



(I)

wherein:

R^1 represents a group selected from:

each ring of which optionally contains a further heteroatom N,
Z represents an optional substituent halogen,
alk represents alkylene or alkenylene,
T represents S, O or NH;

R^2 represents hydrogen, $-C_{1-6}$alkyl, $-C_{1-3}$alkylCONR^{a}R^b, $-C_{1-3}$alkylCO$_2$C$_{1-4}$alkyl, $-CO_2C_{1-4}$alkyl or $-C_{1-3}$alkylCO$_2$H;

R^a and R^b independently represent hydrogen, $-C_{1-6}$alkyl, or together with the N atom to which they are bonded form a 5-, 6- or 7- membered non-aromatic heterocyclic ring optionally containing an additional heteroatom selected from O, N or S, optionally substituted by C_{1-4}alkyl, and optionally the S heteroatom is substituted by O, i.e. represents $S(O)_n$;

X represents phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-2 groups selected from: halogen, $-C_{1-4}$alkyl, $-C_{2-4}$alkenyl, -CN, $-CF_3$, -NR^{a}R^b, $-C_{0-4}$alkylOR^e, -C(O)R^f and -C(O)NR^{a}R^b;

R^e represents hydrogen or $-C_{1-6}$alkyl;

R^f represents $-C_{1-6}$alkyl;

Y represents a group $-C(R^x)(R^z)C_{0-2}$alkylNR^{c}R^d;

R^x represents C_{1-4}alkyl optionally substituted by halogen (e.g. CF_3, $-CH_2CF_3$);

R^z represents hydrogen or C_{1-4}alkyl optionally substituted by halogen (e.g. CF_3, $-CH_2CF_3$);

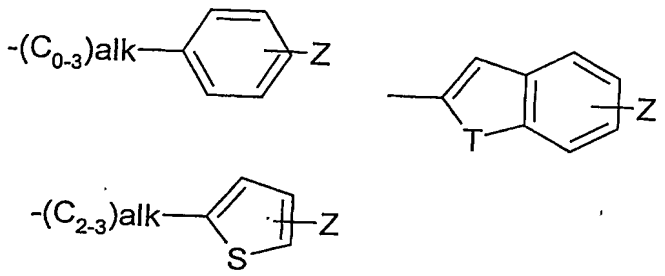
R^c and R^d independently represent hydrogen, $-C_{1-6}$alkyl, $-C_{1-4}$alkylOH, or together with the N atom to which they are bonded form a 5- or 6- membered non-aromatic heterocyclic ring optionally containing an additional heteroatom selected from O, N or S, optionally substituted by C_{1-4}alkyl;

and pharmaceutically acceptable derivatives thereof.

Further aspects of the invention are:

- A pharmaceutical composition comprising a compound of the invention together with a pharmaceutical carrier and/or excipient.
- A compound of the invention for use in therapy.
- Use of a compound of the invention for the manufacture of a medicament for the treatment of a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.
- A method of treating a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor comprising administering a therapeutically effective amount of a compound of the invention.

Preferably, R^1 represents a group selected from:



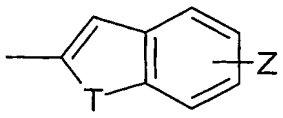
each ring of which optionally contains a further heteroatom N,

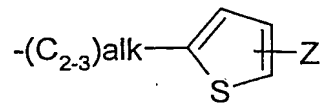
Z represents an optional substituent halogen,

alk represents alkylene or alkenylene,

T represents S, O or NH.

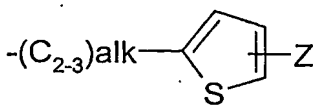
More preferably, R^1 represents a group selected from:





Z represents an optional substituent halogen,
alk represents alkylene or alkenylene.

Even more preferably, R^1 represents a group selected from:



Z represents an optional substituent halogen,
alk represents alkylene or alkenylene.

Preferably, T represents S.

Preferably, R^2 represents hydrogen.

Preferably, R^a and R^b independently represent hydrogen or -C_{1-6}alkyl.

Preferably, X represents phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-2 groups selected from: halogen, -C_{1-4}alkyl or -NR^aR^b. More preferably, X represents phenyl substituted by a halogen. Most preferably, X represents phenyl substituted by a fluorine.

Preferably, Y represents a group -C_{2-3}alkylNR^cR^d. More preferably, Y represents –$C(CH_3)$-NR^cR^d.

Preferably, R^c and R^d independently represent hydrogen, -C_{1-4}alkyl, -C_{1-4}alkylOH, or together with the N atom to which they are bonded form a 6- membered non-aromatic heterocyclic ring optionally containing an additional heteroatom selected from O, N or S. More preferably, R^c represents methyl and R^d represents -C_{1-4}alkyl or -C_{1-4}alkylOH, or R^c and R^d together with the N atom to which they are bonded form a 6- membered non-aromatic heterocyclic ring optionally containing an additional heteroatom selected from O, N or S. Most preferably, R^c represents methyl and R^d represents -C_{1-4}alkyl or -C_{1-4}alkylOH, or R^c and R^d together with the N atom to which they are bonded form a morpholino ring.

It is to be understood that the present invention covers all combinations of preferred, more preferred, even more preferred and most preferred groups described herein above.

As used herein, the term "alkyl" means both straight and branched chain saturated hydrocarbon groups. Examples of alkyl groups include methyl ($-CH_3$), ethyl ($-C_2H_5$), propyl ($-C_3H_7$) and butyl ($-C_4H_9$).

As used herein, the term "alkylene" means both straight and branched chain saturated hydrocarbon linker groups. Examples of alkylene groups include methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$) and propylene ($-CH_2CH_2CH_2-$).

As used herein, the term "alkenylene" means both straight and branched chain unsaturated hydrocarbon linker groups, wherein the unsaturation is present only as double bonds. Examples of alkenylene groups includes ethenylene (-CH=CH-) and propenylene ($-CH_2-CH=CH-$).

As used herein, the term "heterocyclic group" means optionally substituted rings containing one or more heteroatoms selected from: nitrogen, sulphur and oxygen atoms. The heterocycle may be aromatic or non-aromatic, i.e., may be saturated, partially or fully unsaturated. Examples of 5-membered groups include thienyl, furanyl, pyrrolidinyl thiazolyl, oxazolyl and imidazolyl. Examples of 6-membered groups include pyridyl, piperidinyl, pyrimidinyl and morpholinyl. Examples of 7- membered groups include hexamethyleneiminyl. Certain heterocyclic groups, e.g. thienyl, furanyl, thiazolyl, oxazolyl, pyridyl and pyrimidinyl are C-linked to the rest of the molecule. Other heterocyclic groups, e.g pyrrolidinyl, imidazolyl, piperidyl, morpholinyl and hexamethyleneiminyl may be C-linked or N-linked to the rest of the molecule.

As used herein, the term "halogen" means an atom selected from fluorine, chlorine, bromine and iodine.

As used herein, the term "pharmaceutically acceptable" means a compound which is suitable for pharmaceutical use.

As used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester or carbamate, or salt or solvate of such a prodrug, of a compound of formula (I), which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I), or an active metabolite or residue thereof. Preferred pharmaceutically acceptable derivatives are salts, solvates, esters and carbamates. Particularly preferred pharmaceutically

acceptable derivatives are salts, solvates and esters. Most preferred pharmaceutically acceptable derivatives are salts and solvates.

Suitable salts according to the invention include those formed with both organic and inorganic acids and bases. Pharmaceutically acceptable acid addition salts include those formed from mineral acids such as: hydrochloric, hydrobromic, sulphuric, phosphoric, acid; and organic acids such as: citric, tartaric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, formic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic and isethionic acids. Particularly preferred pharmaceutically acceptable salts include those formed from hydrochloric, trifluoroacetic and formic acids.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates of the compound of formula (I) are within the scope of the invention.

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts and solvates.

The compounds of formula (I) contain chiral (asymmetric) centres. The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are within the scope of the present invention. Preferably, the stereochemistry is (S) at the 3-position on the 2-oxopyrrolidine ring (*).

As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference.

Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or in vivo, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxyl or amine groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxyl or amine groups.

Esters may be active in their own right and/or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. An ester may be formed at a carboxylic acid (-COOH) group or a hydroxyl (-OH) group, by methods well known in the art involving reaction with the corresponding alcohol, acid, acid chloride, anhydride, or amide. Preferred esters are C_{1-6}alkyl esters, e.g. methyl esters, ethyl esters, and the like.

Preferred compounds of the invention include:
(*E*)-2-(5-Chloro-2-thienyl)-*N*-(1-{4-[1-(dimethylamino)ethyl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)ethenesulfonamide;
(*E*)-2-(5-Chloro-2-thienyl)-*N*-(1-{4-[1-(dimethylamino)ethyl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)ethenesulfonamide;
(*E*)-2-(5-Chloro-2-thienyl)-*N*-(1-{2-fluoro-4-[1-(4-morpholinyl)ethyl]phenyl}-2-oxo-3-pyrrolidinyl)ethenesulfonamide;
(*E*)-2-(5-Chloro-2-thienyl)-*N*-[1-(2-fluoro-4-{1-[(2-hydroxyethyl)(methyl)amino]ethyl}phenyl)-2-oxo-3-pyrrolidinyl]ethenesulfonamide;
(*E*)-*N*-{1-[4-(1-Aminoethyl)-2-fluorophenyl]-2-oxo-3-pyrrolidinyl}-2-(5-chloro-2-thienyl)ethenesulfonamide; and
6-Chloro-*N*-(1-{4-[1-(dimethylamino)ethyl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)-1-benzothiophene-2-sulfonamide.

Compounds of the invention may show advantageous properties, they may be more efficacious, show greater selectivity, have fewer side effects, have a longer duration of action, be more bioavailable by the preferred route, or have other more desirable properties than similar known compounds.

The compounds of formula (I) are Factor Xa inhibitors and as such are useful in the treatment of clinical conditions susceptible to amelioration by administration of a Factor Xa inhibitor. Such conditions include acute vascular diseases such as acute coronary syndromes (for example primary and secondary prevention of myocardial infarction and

unstable angina and treatment of prothrombotic sequalae associated with myocardial infarction or heart failure), thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty (PTCA), transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke; in preventing thrombosis and complications in patients genetically predisposed to arterial thrombosis or venous thrombosis and patients that have a disease-associated predisposition to thrombosis (e.g. type 2 diabetics); the treatment of pulmonary fibrosis; the treatment of tumour metastasis; inflammation; atherosclerosis; neurogenerative disease such as Parkinson's and Alzheimer's diseases; Kasabach Merritt Syndrome; Haemolytic uremic syndrome; endothelial dysfunction; as anti-coagulants for extracorporeal blood in for example, dialysis, blood filtration, bypass, and blood product storage; and in the coating of invasive devices such as prostheses, artificial valves and catheters in reducing the risk of thrombus formation.

Accordingly, one aspect of the present invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in medical therapy, particularly for use in the amelioration of a clinical condition in a mammal, including a human, for which a Factor Xa inhibitor is indicated.

In another aspect, the invention provides a method for the treatment and/or prophylaxis of a mammal, including a human, suffering from a condition susceptible to amelioration by a Factor Xa inhibitor which method comprises administering to the subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

In another aspect, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of a condition susceptible to amelioration by a Factor Xa inhibitor.

Preferably, the condition susceptible to amelioration by a Factor Xa inhibitor is selected from treatment of acute vascular diseases such as acute coronary syndromes (for example primary and secondary prevention of myocardial infarction and unstable angina and treatment of prothrombotic sequalae associated with myocardial infarction or heart failure), thromboembolism, acute vessel closure associated with thrombolytic therapy and percutaneous transluminal coronary angioplasty, transient ischemic attacks, pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion, prevention of vessel

luminal narrowing (restenosis), and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke.

More preferably, the condition susceptible to amelioration by a Factor Xa inhibitor is selected from acute coronary syndromes (for example primary and secondary prevention of myocardial infarction and unstable angina and treatment of prothrombotic sequalae associated with myocardial infarction or heart failure), pulmonary embolism, deep vein thrombosis and the prevention of thromboembolic events associated with atrial fibrillation, e.g. stroke.

It will be appreciated that reference to treatment includes acute treatment or prophylaxis as well as the alleviation of established symptoms.

While it is possible that, for use in therapy, a compound of the present invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

In a further aspect, the invention provides a pharmaceutical composition comprising at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Accordingly, the present invention further provides a pharmaceutical formulation comprising at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof, in association with a pharmaceutically acceptable carrier and/or excipient. The carrier and/or excipient must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

In another aspect, the invention provides a pharmaceutical composition comprising, as active ingredient, at least one compound of formula (I) or a pharmaceutically acceptable derivative thereof in association with a pharmaceutically acceptable carrier and/or excipient for use in therapy, and in particular in the treatment of human or animal subjects suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.

There is further provided by the present invention a process of preparing a pharmaceutical composition, which process comprises mixing at least one compound of formula (I) or a

pharmaceutically acceptable derivative thereof, together with a pharmaceutically acceptable carrier and/or excipient.

The compounds for use according to the present invention may be formulated for oral, buccal, parenteral, topical, rectal or transdermal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or the nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions or they may be presented as a dry product for constitution with water or other suitable vehicles before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in a conventional manner.

The compounds according to the present invention may be formulated for parenteral administration by injection, e.g. by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds according to the present invention may be formulated for topical administration by insufflation and inhalation. Examples of types of preparation for topical administration include sprays and aerosols for use in an inhaler or insufflator.

Powders for external application may be formed with the aid of any suitable powder base, for example, lactose, talc or starch. Spray compositions may be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as metered dose inhalers, with the use of a suitable propellant.

The compounds according to the present invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously, transcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds according to the present invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

A proposed dose of the compounds according to the present invention for administration to a human (of approximately 70kg body weight) is 0.1mg to 1g, preferably 1mg to 500mg of the active ingredient per unit dose, expressed as the weight of free base. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition to be treated. The dosage will also depend on the route of administration. The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The compounds of formula (I) may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily

appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. The compounds of the present invention may be used in combination with other antithrombotic drugs (such as thrombin inhibitors, thromboxane receptor antagonists, prostacyclin mimetics, phosphodiesterase inhibitors, fibrinogen antagonists, thrombolytic drugs such as tissue plasminogen activator and streptokinase, non-steroidal anti-inflammatory drugs such as aspirin, and the like), anti-hypertensive agents (such as angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, ACE / NEP inhibitors, β-blockers, calcium channel blockers, PDE inhibitors, aldosterone blockers), anti-atherosclerotic / dyslipidaemic agents (such as HMG-CoA reductase inhibitors) and anti-arrhythmic agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations by any convenient route.

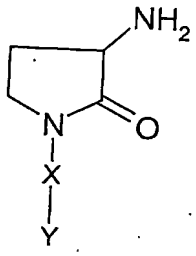
When administration is sequential, either the Factor Xa inhibitor or the second therapeutic agent may be administered first. When administration is simultaneous, the combination may be administered either in the same or different pharmaceutical composition.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation. When formulated separately they may be provided in any convenient formulation, conveniently in such manner as are known for such compounds in the art.

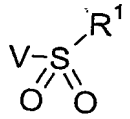
The compounds of formula (I) and pharmaceutically acceptable derivatives thereof may be prepared by the processes described hereinafter, said processes constituting a further aspect of the invention. In the following description, the groups are as defined above for compounds of formula (I) unless otherwise stated.

According to a further aspect of the present invention, there is provided a process (A) for preparing a compound of formula (I) which comprises of reacting a compound of formula (II) or an acid addition salt thereof with a compound of formula (III) where V is a suitable leaving group, such as a halide, preferably chloride. When the free base of a compound of formula (II) is used, the reaction is conveniently carried out in the presence of a base,

e.g. pyridine, and in a suitable solvent, e.g. acetonitrile (MeCN), suitably at 0°C to room temperature. When the acid addition salt of a compound of formula (II) is used, the reaction is conveniently carried out in the presence of a base, e.g. *N,N*-diisopropylethylamine (DIPEA), and in a suitable solvent, e.g. MeCN, suitably at 0°C to room temperature.



(II)

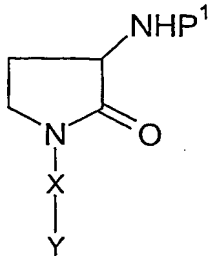


(III)

If X-Y contains a group reactive to compounds of formula (III), such groups may be protected prior to reaction of a compound of formula (II) with a compound of formula (III) using methods well known in the art and such protecting groups removed under standard conditions to provide compounds of formula (I) after completion of the reaction of a compound of formula (II) with a compound of formula (III).

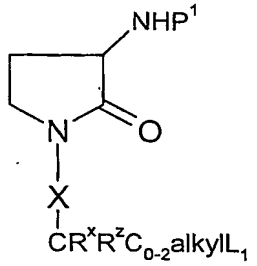
Compounds of formula (III) are known compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

A compound of formula (II) may be prepared from a compound of formula (IV) by removal of the protecting group P^1, e.g. t-butyloxycarbonyl (Boc), under standard conditions. For example, where P^1 represents Boc, removal of the protecting group may be effected under acidic conditions, using for example hydrogen chloride in a solvent such as dioxan.



(IV)

Compounds of formula (IV) may be prepared from compounds of formula (V):

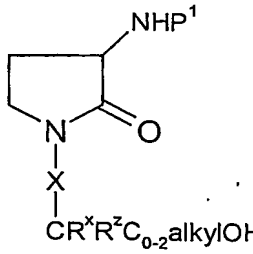


(V)

where L_1 is a suitable leaving group such as halide, e.g. bromide, by reaction with HNR^cR^d, preferably in excess, in a suitable solvent, e.g. tetrahydrofuran (THF), suitably at room temperature.

Compounds of formula HNR^cR^d are known compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

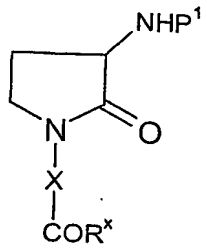
Compounds of formula (V) may be prepared from compounds of formula (VI):



(VI)

by halogenation methods well known to persons skilled in the art. For example, when L_1 is bromide, bromination may be effected with carbon tetrabromide, in a suitable solvent, e.g. dichloromethane (DCM), in the presence of a phosphine,e.g. triphenylphosphine, suitably at 0°C to room temperature.

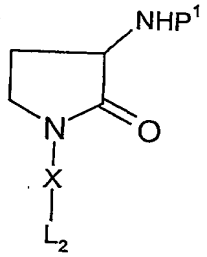
Compounds of formula (VI), where $CR^xR^zC_{0-2}$alkylOH represents CR^xHOH, may be prepared from compounds of formula (VII):



(VII)

- by reduction under standard conditions, e.g. by treatment with a nucleophilic hydride source, e.g. sodium borohydride, in a suitable solvent, e.g. methanol, suitably at 0°C to room temperature.

Compounds of formula (VII) may be prepared from compounds of formula (VIII):

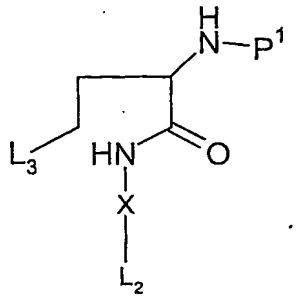


(VIII)

where L_2 is a suitable leaving group such as halide, e.g. iodide, by reaction with a suitable vinyl ether, e.g. n-butyl vinyl ether, in the presence of a base, e.g. sodium carbonate and triethylamine, in a suitable solvent, e.g. N,N-dimethylformamide (DMF), in the presence of a metal catalyst, e.g. palladium(II) acetate, and a suitable ligand, e.g. 1,3-bis(diphenylphosphino)propane, suitably at elevated temperature (e.g. 60-110°C) and suitably under an inert atmosphere, e.g. nitrogen; followed by hydrolysis with an appropriate aqueous acid, e.g. aqueous formic acid, in a suitable solvent, e.g. MeCN, suitably at room temperature.

Vinyl ethers are known compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

Compounds of formula (VIII) may be prepared from compounds of formula (IX):

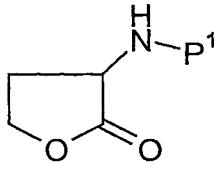


(IX)

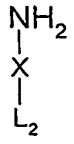
by cyclisation where L_3 represents a suitable leaving group, e.g. hydroxyl. For example when L_3 is a hydroxyl group, the ring closure may be performed by treatment with a mixture of (i) aryl or alkyl phosphine, e.g. tri-n-butylphosphine, and (ii) a suitable azodicarboxylate derivative, e.g. 1,1'-(azodicarbonyl)-dipiperidine, in a suitable solvent, e.g. THF, suitably at room temperature.

It will be appreciated by persons skilled in the art that compounds of formula (IX) may be prepared by interconversion, utilising other compounds of formula (IX) which are optionally protected by standard protecting groups, as precursors. For instance, compounds of formula (IX) where L_3 is OH, may be converted into compounds of formula (IX) possessing alternative substituents at L_3, e.g. halogen, $S^+MeR\ W^-$ or OSO_2R, by methods well known in the art (see for example Smith, M.B. and March, J., Advanced Organic Chemistry, 5th Edition 2001, John Wiley & Sons). Generally R will represent alkyl or aralkyl and W will represent sulphate or halide, especially iodide. In such cases the ring closure may be performed by treatment with a base in a suitable solvent, e.g. MeCN.

Compounds of formula (IX), where L_3 is a hydroxyl group, may be prepared by reacting a compound of formula (X) with a compound of formula (XI):



(X)

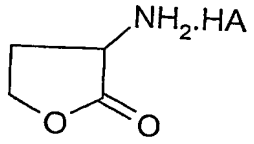


(XI)

wherein P^1 is a suitable protecting group as described above. The reaction is conveniently carried out by addition of a suitable activating agent, e.g. trimethylaluminium, to compounds of formula (XI) in a suitable solvent, e.g. DCM, under an inert atmosphere, e.g. nitrogen, suitably at room temperature followed by addition of a compound of formula (X) in a compatible solvent, e.g. DCM.

Compounds of formula (XI) are known compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

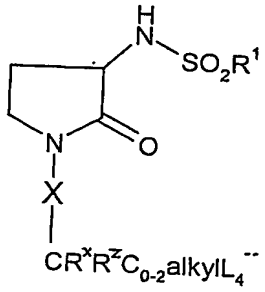
Compounds of formula (X) may be prepared from compounds of formula (XII) where HA is a suitable acid, e.g. hydrochloric acid, using methods well known to those skilled in the art. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994).



(XII)

Compounds of formula (XII) are known compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

There is provided a further process (B) for preparing compounds of formula (I). According to process (B), compounds of formula (I) may be prepared from compounds of formula (XIII):

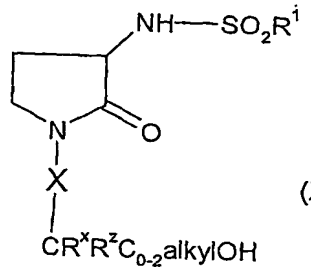


(XIII)

where L_4 is a suitable leaving group, such as halide, e.g. bromide, by reaction with HNR^cR^d, preferably in excess, in a suitable solvent, e.g. THF, suitably at room temperature to 60°C.

Alternatively, compounds of formula (I) where R^c and R^d independently represent hydrogen may be prepared from compounds of formula (XIII) by reaction with sodium diformamide in a suitable solvent, e.g. DMF, suitably at elevated temperature, e.g. 40-60°C, followed by hydrolysis with an appropriate aqueous acid, e.g. hydrochloric acid (HCl), suitably at elevated temperature, e.g. 40-60°C.

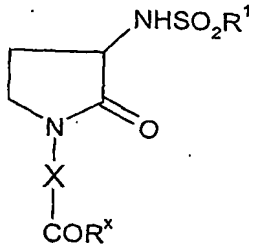
Compounds of formula (XIII) may be prepared from compounds of formula (XIV):



(XIV)

by halogenation methods well known to persons skilled in the art. For example, when L_4 is bromide, bromination may be effected with carbon tetrabromide, in a suitable solvent, e.g. DCM, in the presence of a phosphine e.g. triphenylphosphine, suitably at 0°C to room temperature.

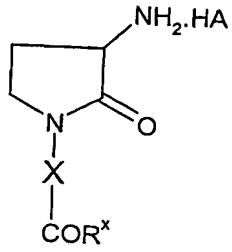
Compounds of formula (XIV), where $CR^xR^zC_{0-2}$alkylOH represents CR^xHOH, may be prepared from compounds of formula (XV):



(XV)

by reduction under standard conditions, e.g. by treatment with a nucleophilic hydride source, e.g. sodium borohydride in a suitable solvent, e.g. methanol, suitably at 0°C to room temperature.

Compounds of formula (XV) may be prepared by reaction of compounds of formula (XVI) where HA is a suitable acid, e.g. hydrochloric acid:



(XVI)

with compounds of formula (III), where V is a suitable leaving group, such as a halide, preferably chloride. The reaction is conveniently carried out in the presence of a base, e.g. DIPEA, and in a suitable solvent, e.g. MeCN, suitably at room temperature.

Compounds of formula (XVI) may be prepared from compounds of formula (VII) by removal of the protecting group P^1, e.g. t-butyloxycarbonyl (Boc), under standard conditions. For example, where P^1 represents Boc, removal of the protecting group may be effected under acidic conditions, using for example hydrogen chloride in a solvent such as dioxan.

There is provided a further process (C) for preparing compounds of formula (I) where R^2 is a substituent other than hydrogen, which comprises reacting a compound of formula (I) where R^2 is hydrogen with a compound of formula (XVII):

$$R^2—T \qquad \text{(XVII)}$$

wherein R^1 and R^2 are defined as above and T is a suitable leaving group such as that derived from a hydroxyl group or halide, e.g. bromide. When T is halide, the reaction is effected in a suitable organic solvent, e.g. THF or DMF, in the presence of a base, e.g. LiHMDS, potassium carbonate or sodium carbonate at a temperature range from -78°C to +50°C, preferably -78°C to room temperature. Furthermore, it will appreciated that the substituent R^2, other than hydrogen, may be introduced at various intermediate stages by methods well known to those skilled in the art. When T is a hydroxyl group, the reaction is effected under Mitsunobu conditions (for examples see Hughes, David L. Progress in the Mitsunobu reaction. A review. Organic Preparations and Procedures International (1996), 28(2), 127-64.). For example, the reaction may be performed by treatment of compounds of formula (I) where R^2 represents H with an aryl or alkyl phosphine, e.g. triphenylphosphine, optionally bound to polymer-support, and an azodicarboxylate derivative, e.g. di-*tert*-butyl azodicarboxylate, in a suitable solvent, e.g. THF, followed by

addition of a compound of formula (XVII) where T represents OH, optionally in a suitable solvent, e.g. THF, suitably at room temperature.

When X-Y contains a group reactive to compounds of formula (XVII), such groups may be protected prior to the reaction using methods well known in the art and such protecting groups removed under standard conditions to provide compounds of formula (I) where R^2 is a substituent other than hydrogen after completion of the reaction of a compound of formula (I) where R^2 is hydrogen with a compound of formula (XVII).

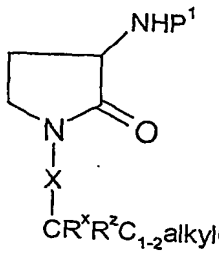
Compounds of formula (XVII) are known compounds or may be prepared by methods known in the literature or processes known to those skilled in the art.

Furthermore, it will appreciated that the substituent R^2, other than hydrogen, may be introduced at various intermediate stages by methods well known to those skilled in the art.

Compounds of formula (I) where R^c and/or R^d are hydrogen may be converted to other compounds of formula (I) by processes known to those skilled in the art, for example, where R^c and/or R^d are converted to C_{1-4}alkyl by reductive alkylation.

There is provided a further process (D) for preparing compounds of formula (I). According to process (D), compounds of formula (I) where R^z is not hydrogen may be prepared from compounds of formula (VII) by reaction with an amine HNR^cR^d in a suitable solvent e.g. DCM, to form an intermediate imine or iminium species which is then reacted with a suitable organometallic agent e.g. a Grignard reagent in a suitable solvent e.g. THF suitably at 0°C to room temperature.

According to a further process (E) compounds of formula (VI) where C_{0-2}alkyl represents C_{1-2}alkyl may be preapred from compounds of formula (XVIII)

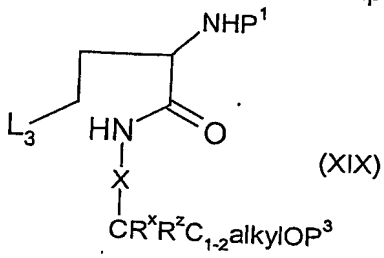


(XVIII)

where P^3 is a suitable hydroxyl protecting group, by removal of the protecting group under standard conditions using methods well known to those skilled in the art. See, for

example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994).

Compounds of formula (XVIII) may be prepared from compounds of formula (XIX):

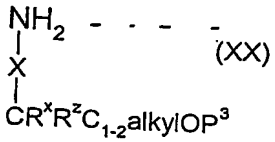


(XIX)

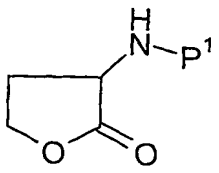
by cyclisation where L_3 represents a suitable leaving group. For example when L_3 is a hydroxyl group, the ring closure may be performed by treatment with a mixture of (i) aryl or alkyl phosphine, e.g. tri-n-butylphosphine, and (ii) a suitable azodicarboxylate derivative, e.g. 1,1'-(azodicarbonyl)-dipiperidine, in a suitable solvent, e.g. THF, suitably at room temperature.

It will be appreciated by persons skilled in the art that compounds of formula (XIX) may be prepared by interconversion, utilising other compounds of formula (XIX) which are optionally protected by standard protecting groups, as precursors. For instance, compounds of formula (XIX) where L_3 is OH, may be converted into compounds of formula (XIX) possessing alternative substituents at L_3, e.g. halogen, $S^+MeR\ W^-$ or OSO_2R, by methods well known in the art (see for example Smith, M.B. and March, J., Advanced Organic Chemistry, 5th Edition 2001, John Wiley & Sons). Generally R will represent alkyl or aralkyl and W will represent sulphate or halide, especially iodide. In such cases the ring closure may be performed by treatment with a base in a suitable solvent, e.g. MeCN.

Compounds of formula (XIX), where L_3 is a hydroxyl group, may be prepared by reacting a compound of formula (XX) with a compound of formula (X):



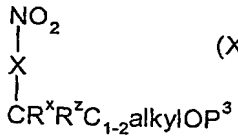
(XX)



(X)

wherein P^1 is a suitable protecting group as described above. The reaction is conveniently carried out by addition of a suitable activating agent, e.g. trimethylaluminium, to compounds of formula (XX) in a suitable solvent, e.g. DCM, under an inert atmosphere, e.g. nitrogen, suitably at room temperature followed by addition of a compound of formula (X) in a compatible solvent, e.g. DCM.

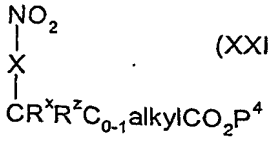
Compounds of formula (XX) may be prepared from compounds of formula (XXI)



(XXI)

Compounds of formula (XX) may be prepared by methods known in the art, e.g. from compounds of formula (XXI) by hydrogenation in the presence of a suitable catalyst e.g. 10% palladium on carbon, in a suitable solvent such as ethanol, suitably at atmospheric pressure and room temperature.

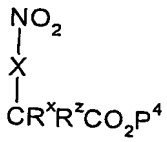
Compounds of formula (XXI), where P^3 is a suitable protecting group, may be prepared from compounds of formula (XXII) where P^4 is a hydrogen or an alkyl or aralkyl group by reduction processes well-known to those skilled in the art. For example, when P^4



(XXII)

represents a hydrogen, compounds of formula (XXI) may be prepared by reduction with a hydride source, e.g., diborane, in a suitable solvent, e.g., THF, suitably at 0 °C to room temperature followed by protection with a suitable P^3 protecting group using methodologies well known to those skilled in the art. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994).

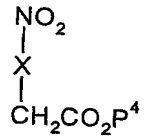
Compounds of formula (XXII), where C_{0-1}alkyl represents C_1alkyl, may be prepared from compounds of formula (XXIII), where P^4 is a hydrogen, by chain extension processes well-known to those skilled in the art.



(XXIII)

For example, compounds fo formula (XXII) where C_{0-1}alkyl represents C_1alkyl, and P^4 is a hydrogen, may be prepared from compounds of formula (XXIII), where P^4 is a hydrogen , via the Arndt-Eistert synthesis. For example, compounds of formula (XXII) where C_{0-1}alkyl represents C_1alkyl, and P^4 is a hydrogen, may be prepared from compounds of formula (XXIII), where P^4 is a hydrogen, by activation to an acid halide, e.g., acid chloride, using standard methodologies, followed by reaction with diazomethane in a suitable solvent, e.g., diethyl ether, suitably at 0 °C to room temperature, followed by Wolff rearrangement with a silver salt, e.g., silver oxide, and water, optionally in the presence of a base, e.g., triethylamine, in a suitable solvent .

Compound of formula (XXIII), where P^4 is a suitable carboxylic acid protecting group, may be prepared from compounds of formula (XXIV) by alkylation chemistries



(XXIV)

well known in the art (see for example Smith, M.B. and March, J., Advanced Organic Chemistry, 5th Edition 2001, John Wiley & Sons).

Compounds of formula (XXIV) are known compounds or may be prepared by methods known-in-the literature or processes known to those skilled in the art.

It will be appreciated by those skilled in the art that compounds of formula (I) or a solvate thereof may be synthesized from appropriate intermediates via solid phase chemistry processes.

Those skilled in the art will appreciate that in the preparation of the compound of formula (I) or a solvate thereof it may be necessary and/or desirable to protect one or more sensitive groups in the molecule or the appropriate intermediate to prevent undesirable side reactions. Suitable protecting groups for use according to the present invention are well known to those skilled in the art and may be used in a conventional manner. See, for example, "Protective groups in organic synthesis" by T.W. Greene and P.G.M. Wuts (John Wiley & sons 1991) or "Protecting Groups" by P.J. Kocienski (Georg Thieme Verlag 1994). Examples of suitable amino protecting groups include acyl type protecting groups (e.g. formyl, trifluoroacetyl, acetyl), aromatic urethane type protecting groups (e.g. benzyloxycarbonyl (Cbz) and substituted Cbz), aliphatic urethane protecting groups (e.g. 9-fluorenylmethoxycarbonyl (Fmoc), t-butyloxycarbonyl (Boc), isopropyloxycarbonyl, cyclohexyloxycarbonyl) and alkyl or aralkyl type protecting groups (e.g. benzyl, trityl, chlorotrityl). Examples of suitable hydroxyl protecting groups may include for example alkyl silyl groups, such as trimethylsilyl or tert-butyldimethylsilyl; alkyl ethers such as tetrahydropyranyl or tert-butyl; or esters such as acetate. Examples of carboxylic acid protecting groups may include for example aralkyl groups, e.g. benzyl, or alkyl groups, e.g. t-butyl.

Various intermediate compounds used in the above-mentioned process, including but not limited to certain compounds of formulae (II), (IV), (V), (VI), (VII), (VIII), (XIII), (XIV), (XV), (XVI), (XVIII), (XIX), (XX), (XXI), (XXII) and (XXIII) are novel and accordingly constitute a further aspect of the present invention.

The present invention will now be further illustrated by the accompanying examples which should not be construed as limiting the scope of the invention in any way.

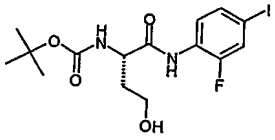
All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Examples

Abbreviations

THF	Tetrahydrofuran
MeCN	Acetonitrile
DCM	Dichloromethane
DMF	*N,N*-Dimethylformamide
DIPEA	*N,N*-Diisopropylethylamine
Boc	t-butyloxycarbonyl
CBZ	carbobenzyloxy

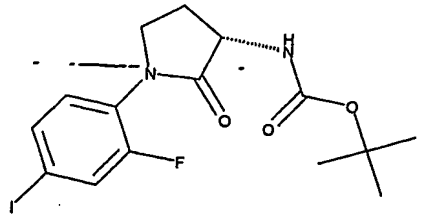
Intermediate 1



1,1-Dimethylethyl ((1*S*)-1-{[(2-fluoro-4-iodophenyl)amino]carbonyl}-3-hydroxypropyl)-carbamate

A solution of 2-fluoro-4-iodoaniline (7.11g) in anhydrous DCM (40ml) under N_2 at 0°C was treated dropwise with trimethylaluminium (2N in heptane; 15ml). The mixture was allowed to stir for 30min before a solution of 1,1-dimethylethyl [(3*S*)-2-oxotetrahydro-3-furanyl]carbamate (5.03g), in anhydrous DCM (35ml), was added dropwise. The reaction was allowed to warm up to ambient temperature and stirred for 18h, before quenching with 10% aqueous citric acid (10ml). Saturated aqueous potassium sodium tartrate (100ml) was then added with stirring followed by separation of the organic and aqueous layers. The organic layer was dried (over magnesium sulphate) and concentrated under reduced pressure. The residue was purified using Biotage™ chromatography (silica, eluting with cyclohexane:ethyl acetate 3:2) to afford an off-white solid which was an inseparable mixture (*c.* 1:2) of the starting material and the title compound (5.55g).
Mass spectrum: Found: MH^+ 439

Intermediate 2

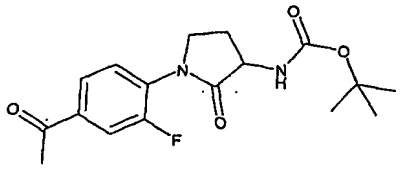


1,1-Dimethylethyl [(3*S*)-1-(2-fluoro-4-iodophenyl)-2-oxo-3-pyrrolidinyl]carbamate

To a solution of crude Intermediate 1 (5.55g) and tri-n-butylphosphine (3.49ml) in anhydrous THF (100ml) under N_2 at 0°C was added solid 1,1'-(azodicarbonyl)-dipiperidine (3.53g). The solution was allowed to warm to ambient temperature and stirred for 18h. The mixture was then diluted with cyclohexane (100ml) and the precipitate filtered off. The filtrate was then concentrated under reduced pressure and the residue purified using Biotage™ chromatography (silica, eluting with cyclohexane:ethyl acetate 2:1) to give the title compound (2.93g) as a white solid.

Mass spectrum: Found: MH^+ 421

Intermediate 3

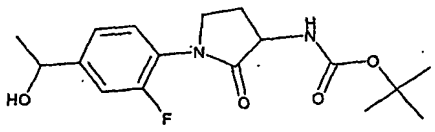


1,1-Dimethylethyl [1-(4-acetyl-2-fluorophenyl)-2-oxo-3-pyrrolidinyl]carbamate

A degassed solution of Intermediate 2 (1.05g) in dry DMF (20ml) was treated sequentially with sodium carbonate (0.42g), triethylamine (0.67ml), n-butyl vinyl ether (1.62ml), 1,3-bis(diphenylphosphino)propane (0.124g) and palladium(II) acetate (0.034g). The mixture was heated to 80°C under nitrogen for 7h, allowing to cool and stirred overnight. Solvent was removed under reduced pressure and the crude residue treated with 0.1% formic acid: water (10ml) and MeCN (10ml). The mixture was stirred at ambient temperature for 4h before concentrating under reduced pressure. The residue was dissolved in minimum DCM and purified using pre-conditioned silica phase SPE (20g/60cc) eluting with cyclohexane: ethyl acetate (5:1 to neat ethyl acetate) to give the title compound (0.362g) as a yellow powder.

Mass spectrum: Found: MH^+ 337

Intermediate 4



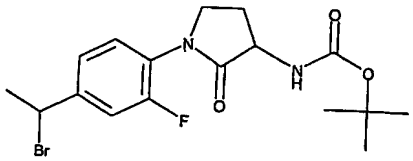
1,1-Dimethylethyl {1-[2-fluoro-4-(1-hydroxyethyl)phenyl]-2-oxo-3-pyrrolidinyl}carbamate

Intermediate 3 (110mg) in dry methanol (4ml) was treated with sodium borohydride (0.012g) and the mixture stirred at ambient temperature for 18h under nitrogen. The reaction was quenched with 3 drops water and concentrated under reduced pressure, partitioning the residue between DCM and water. The separated organic layer was dried (hydrophobic frits) and concentrated under reduced pressure to give the title compound (0.103g) as a cream solid.

Mass spectrum: Found: MH^+ 339

H.p.l.c. R_t 2.61min

Intermediate 5

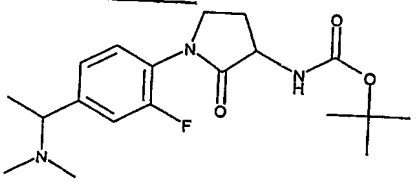


1,1-Dimethylethyl {1-[4-(1-bromoethyl)-2-fluorophenyl]-2-oxo-3-pyrrolidinyl}carbamate

Intermediate 4 (0.103g) in dry DCM (6ml) at 0°C was treated with carbon tetrabromide (0.119g) and stirred for 3min. To the mixture was added triphenylphosphine (0.094g) in portions and the reaction stirred at 0°C for 1.5h before more carbon tetrabromide (0.119g) and triphenylphosphine (0.094g) were added. The reaction was warmed up to ambient temperature and stirred overnight under nitrogen. The mixture was diluted with DCM and washed with water. The separated organic layer was dried (hydrophobic frits) and concentrated under reduced pressure, to a small volume, and purified using pre-conditioned Silica phase SPE (5g/20cc) eluting with cyclohexane: ethyl acetate (4:1 to 2:1) to give the title compound (0.026g) as a cream solid.

Mass spectrum: Found: MH^+ 403

Intermediate 6

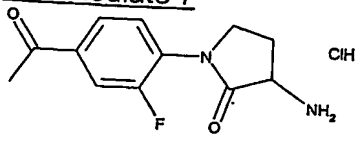


1,1-Dimethylethyl (1-{4-[1-(dimethylamino)ethyl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)carbamate

Intermediate 5 (0.027g) was treated with 2N dimethylamine in THF (3ml) and stirred for 18h at ambient temperature. Solvent was removed under reduced pressure and the residue partitioned between chloroform and saturated aqueous sodium bicarbonate solution. The separated organic layer was dried (hydrophobic frits) and re-concentrated under reduced pressure. The residue was purified using SCX SPE (1g/2ml) eluting with DCM to 10%ammonia/methanol to give the title compound (0.019g) as a sticky gum.

Mass spectrum: Found: MH^+ 366

Intermediate 7

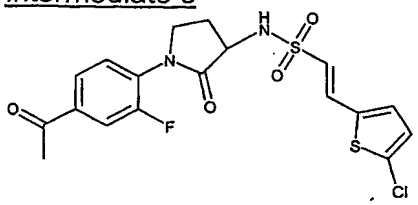


1-(4-Acetyl-2-fluorophenyl)-3-amino-2-pyrrolidinone hydrochloride

Intermediate 3 (0.156g) was stirred in 4M hydrogen chloride / dioxane (6ml) at ambient temperature for 2h. The reaction was concentrated under reduced pressure to give the title compound (0.135g) as a pale yellow solid.

Mass spectrum: Found: MH^+ 237

Intermediate 8



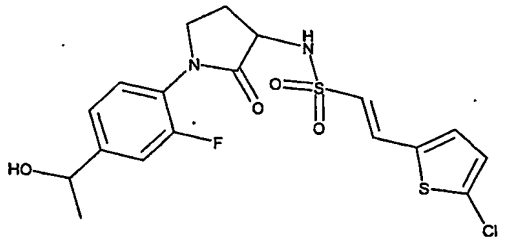
(*E*)-*N*-[1-(4-Acetyl-2-fluorophenyl)-2-oxo-3-pyrrolidinyl]-2-(5-chloro-2-thienyl)ethenesulfonamide

Using Intermediate 7 (0.135g), suspended in dry acetonitrile (5ml) was cooled to 0°C and treated with DIPEA (0.19ml), allowing to stir for 5min. A pre-cooled solution of (E)-2-(2-chlorothiophene)-1-ethenesulphonyl chloride (0.122g) in dry acetonitrile (2ml) was added slowly and the mixture stirred at 0°C for 2h before warming up to ambient temperature and stirring overnight. The mixture was concentrated under reduced pressure, partitioning the residue between DCM and Aq saturated sodium bicarbonate. The separated organic layer was dried (hydrophobic frits) concentrating the filtrate under reduced pressure to give the title compound (0.162g) as a pale yellow solid.

Mass spectrum: Found: $(M-H)^-$ 441

H.p.l.c. R_t 3.16min

Intermediate 9

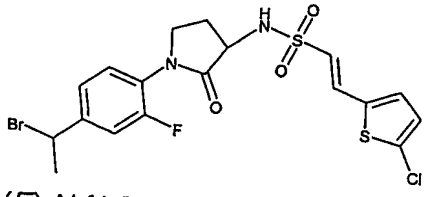


(*E*)-2-(5-chloro-2-thienyl)-*N*-{1-[2-fluoro-4-(1-hydroxyethyl)phenyl]-2-oxo-3-pyrrolidinyl}ethenesulfonamide

Intermediate 8 (0.163g) suspended in dry methanol (5ml) was treated with sodium borohydride (0.028g) and the mixture stirred at ambient temperature for 90min under nitrogen. The reaction was quenched with 3 drops water and concentrated under reduced pressure, partitioning the residue between DCM and water. The separated organic layer

was dried (hydrophobic frits) and concentrated under reduced pressure to give the title compound (0.149g) as a beige foamy solid.
Mass spectrum: Found: MH^+ 445
H.p.l.c. R_t 3.00min

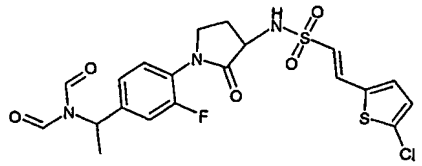
Intermediate 10



(*E*)-*N*-{1-[4-(1-Bromoethyl)-2-fluorophenyl]-2-oxo-3-pyrrolidinyl}-2-(5-chloro-2-thienyl)ethenesulfonamide

A solution of Intermediate 9 (0.149g) in dry DCM (6ml) at 0°C was treated with carbon tetrabromide (0.136g) and stirred for 5min. To the mixture was added triphenylphosphine (0.106g) in portions and the reaction stirred at 0°C for 2h before more carbon tetrabromide (0.136g) and triphenylphosphine (0.106g) were added. The reaction was warmed up to ambient temperature and stirred overnight under nitrogen. The mixture was diluted with DCM and washed with water. The separated organic layer was dried (hydrophobic frits) and concentrated under reduced pressure, to a small volume, and purified using pre-conditioned silica phase SPE (5g/20cc) eluting with cyclohexane: ethyl acetate (10:1 to 2:1) to give the title compound (0.09g) as a beige solid.
Mass spectrum: Found $(M-H)^-$ 506

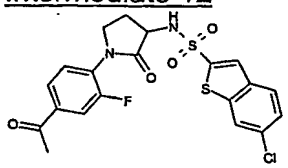
Intermediate 11



(*E*)-2-(5-chloro-2-thienyl)-*N*-(1-{4-[1-(diformylamino)ethyl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)ethenesulfonamide

A solution of Intermediate 10 (0.09g), in dry DMF (4ml), was treated with sodium diformamide (0.019g) and then heated to 50°C under nitrogen for 3.5h. The reaction was cooled to ambient temperature and the solvent removed under reduced pressure, partitioning the residue between DCM and water. The separated organic layer was dried (hydrophobic frits) and re-concentrated under reduced pressure to give the title compound (0.075g) as an orange gum.
Mass spectrum: Found: $(M-H)^-$ 498

Intermediate 12

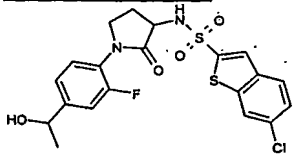


N-[1-(4-Acetyl-2-fluorophenyl)-2-oxo-3-pyrrolidinyl]-6-chloro-benzothiophene-2-sulfonamide

The title compound was prepared from Intermediate 7 and 6-chloro-1-benzothiophene-2-sulphonyl chloride using the synthetic procedure described for Intermediate 8.

Mass spectrum: Found: MH^+ 467

Intermediate 13

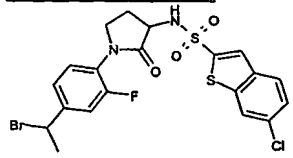


6-Chloro-*N*-{1-[2-fluoro-4-(1-hydroxyethyl)phenyl]-2-oxo-3-pyrrolidinyl}-1-benzothiophene-2-sulfonamide

The title compound was prepared from Intermediate 12 using the synthetic procedure described for Intermediate 9.

Mass spectrum: Found: MH^+ 469

Intermediate 14

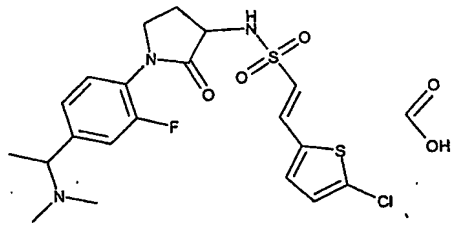


N-{1-[4-(1-Bromoethyl)-2-fluorophenyl]-2-oxo-3-pyrrolidinyl}-6-chloro-1-benzothiophene-2-sulfonamide

The title compound was prepared from Intermediate 13 using the synthetic procedure described for Intermediate 10.

Mass spectrum: Found: MH^+ 531

Example 1



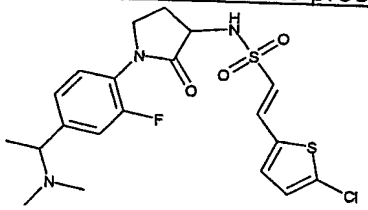
Formic acid - (*E*)-2-(5-chloro-2-thienyl)-*N*-(1-{4-[1-(dimethylamino)ethyl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)ethenesulfonamide (1:1)

Intermediate 6 (0.019g) was stirred in 4M hydrogen chloride/ dioxane (3ml) at ambient temperature for 2h. The reaction was concentrated under reduced pressure to give an off white gum (0.019g). This material in dry MeCN (2ml) at 0°C was treated with DIPEA (0.031ml). The reaction was stirred for 5 min before a pre-cooled solution of (E)-2-(2-chlorothiophene)-1-ethenesulphonyl chloride (0.0136g) in dry MeCN (2ml) was added in dropwise manner. Upon completion of addition, the mixture was stirred at 0°C for 2h, then warmed up and stirred at room temperature for 6h under nitrogen. Solvent was removed under reduced pressure and the residue partitioned between DCM and saturated aqueous sodium bicarbonate solution. The separated organic layer was washed with water, dried (hydrophobic frits) and concentrated under reduced pressure. The residue was purified by mass directed preparative h.p.l.c. to give the title compound (0.021g) as a white powder.

Mass spectrum: Found: MH^+472

H.p.l.c. R_t 2.38min

Example 1 (alternative procedure)



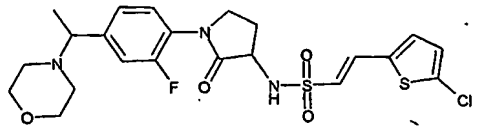
(*E*)-2-(5-chloro-2-thienyl)-*N*-(1-{4-[1-(dimethylamino)ethyl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)ethenesulfonamide

Intermediate 10 (0.066g) in dry THF (4ml) was treated with a 2N solution of dimethylamine in THF (0.143ml). The reaction was stirred at room temperature for 1 ½ h. After this period the reaction was heated to 45°C for 3h, before cooling to room temperature and stirring for 72h. The mixture was concentrated under reduced pressure, partitioning the residue between DCM and saturated aqueous sodium bicarbonate solution. The separated organic layer was washed with water, dried (hydrophobic frits) and concentrated under reduced pressure. The residue was loaded onto a pre conditioned SCX cartridge (2g/12cc)eluting the product with 10% aqueous ammonia-/-methanol to give the title compound (0.021g) as a pink gummy solid.

Mass spectrum: Found: MH^+472

H.p.l.c. R_t 2.34min

Example 2



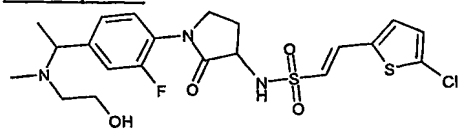
(*E*)-2-(5-Chloro-2-thienyl)-*N*-(1-{2-fluoro-4-[1-(4-morpholinyl)ethyl]phenyl}-2-oxo-3-pyrrolidinyl)ethenesulfonamide

A solution of Intermediate 10 (30mg) in dry THF (3ml) was treated with morpholine (26ul). The mixture was heated to 45°C for 18h, before allowing cooling to ambient temperature. Solvent was removed under reduced pressure and the residue partitioned between chloroform and saturated aqueous sodium bicarbonate solution. The separated organic layer was dried (hydrophobic frits) and re-concentrated under reduced pressure. The residue was purified by mass directed preparative h.p.l.c. to give the title compound (0.018g) as a white powder.

Mass spectrum: Found: MH^+ 514

H.p.l.c. R_t 2.42min

Example 3



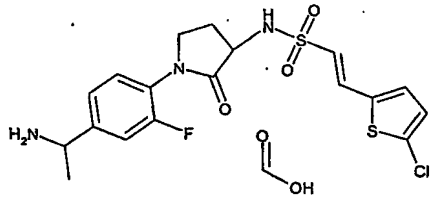
(*E*)-2-(5-Chloro-2-thienyl)-*N*-[1-(2-fluoro-4-{1-[(2-hydroxyethyl)(methyl)amino]ethyl}phenyl)-2-oxo-3-pyrrolidinyl]ethenesulfonamide

Using Intermediate 10 and the procedure described in Example 2, the title compound was prepared.

Mass spectrum: Found: MH^+ 502

H.p.l.c. R_t 2.36min

Example 4

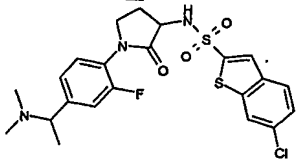


Formic acid - (*E*)-*N*-{1-[4-(1-aminoethyl)-2-fluorophenyl]-2-oxo-3-pyrrolidinyl}-2-(5-chloro-2-thienyl)ethenesulfonamide (1:1)

Intermediate 11 (0.065g) was treated with 6N aqueous hydrochloric acid (5ml). The mixture was stirred at ambient temperature for 18h, then heated to 50°C for 3h, before allowing cooling to ambient temperature. Solvent was removed under reduced pressure and the residue partitioned between DCM and saturated aqueous sodium bicarbonate solution. The separated organic layer was dried (hydrophobic frits) and re-concentrated

under reduced pressure. The residue was purified by mass directed preparative h.p.l.c. to give the title compound (0.011g) as a white powder.
Mass spectrum: Found: MH^+ 444
H.p.l.c. R_t 2.40min

Example 5



6-Chloro-*N*-(1-{4-[1-(dimethylamino)ethyl]-2-fluorophenyl}-2-oxo-3-pyrrolidinyl)-1-benzothiophene-2-sulfonamide

The title compound was prepared from Intermediate 14 at room temperature using a similar synthetic procedure to that described for Example 1 (alternative procedure).
Mass spectrum: Found: MH^+ 496
H.p.l.c. R_f 2.44min

In vitro assay for inhibition of Factor Xa

Compounds of the present invention were tested for their Factor Xa inhibitory activity as determined *in vitro* by their ability to inhibit human Factor Xa in a fluorogenic assay, using Rhodamine 110, bis-CBZ-glycylglycyl-L-arginine amide as the fluorogenic substrate. Compounds were diluted from a 10mM stock solution in dimethylsulfoxide at appropriate concentrations. Assay was performed at room temperature using buffer consisting of: 50mM Tris-HCl, 150mM NaCl, 5mM $CaCl_2$, pH 7.4. containing human Factor Xa (final conc. Of 0.0003U.ml-1). Compound and enzyme were preincubated for 15min prior to addition of the substrate (final conc. of 10 μM). The reaction was stopped after 3 hrs with the addition of H-D-Phe-Pro-Arg-Chloromethylketone. An LJL-Analyst fluorimeter was used to monitor fluorescence with 485 nm excitation/535 nm emission. To obtain IC_{50} values the data were analysed using ActivityBase® and XLfit®.

Calculation of Ki values:
$Ki = IC_{50}/(1 + [Substrate]/Km)$
The Ki value for the above assay can be obtained by dividing the IC_{50} value by 1.6.

All of the synthetic Example compounds tested by the above described *in vitro* assay were found to exhibit Factor Xa inhibitory activity. Preferably compounds have a Ki value of less than 1μM (Examples 1, 2, 3, 4). More preferably, compounds have a Ki value of less than 0.1μM (Examples 1, 2, 3, 4). Most preferably, compounds have a Ki value of less than 10nM (Examples 1, 2, 3, 4).

Method for measurement of Prothrombin Time (PT)

Blood was collected into a sodium citrate solution (ratio 9:1) to give a final concentration of 0.38% citrate. Plasma was generated by centrifugation of citrated blood samples at 1200 x g for 20 min at 4°C and stored at -20°C until use. PT analysis was conducted using plasma pooled from 4 separate donors (2 male and 2 female).

The PT test was performed using the BCS Coagulation Analyzer (Dade Behring). For assay, 50 ul of plasma containing test compound at concentrations ranging from 0.03 to 100 uM (made from a 100 uM stock containing 1% DMSO in plasma) was combined with 100 ul of Thromboplastin C Plus (Dade Behring). Upon addition of the reagents, absorbance at 405 nm was monitored and time to clot formation is determined (normal range for human plasma is 10.6-12.4 seconds).

All of the synthetic Example compounds tested by the above described assay were found to exhibit activity.

General purification and analytical methods

LC/MS Method

Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3µm, 3.3cm x 4.6mm ID) eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 95% MeCN and 0.05% HCO_2H in water (solvent B), using the following elution gradient 0-0.7 minutes 0%B, 0.7-4.2 minutes 0→100%B, 4.2-5.3 minutes 100%B, 5.3-5.5 minutes 100→0%B at a flow rate of 3 ml/minutes (System 1). The mass spectra (MS) were recorded on a Fisons VG Platform mass spectrometer using electrospray positive ionisation [(ES+ve to give MH^+ and $M(NH_4)^+$ molecular ions] or electrospray negative ionisation [(ES-ve to give $(M-H)^-$ molecular ion] modes.

^1H nmr spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the external standard.

Biotage™ chromatography refers to purification carried out using equipment sold by Dyax Corporation (either the Flash 40i or Flash 150i) and cartridges pre-packed with KPSil.

Mass directed autoprep refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5µm column (5cm x 10mm i.d.) with 0.1% HCO_2H in water and 95% MeCN, 5% water (0.5% HCO_2H) utilising the following

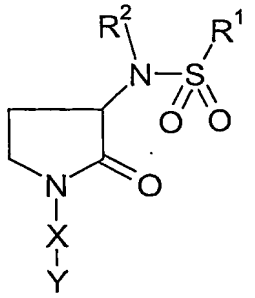
gradient elution conditions: 0-1.0 minutes 5%B, 1.0-8.0 minutes 5→30%B, 8.0-8.9 minutes 30%B, 8.9-9.0 minutes 30→95%B, 9.0-9.9 minutes 95%B, 9.9-10 minutes 95→0%B at a flow rate of 8ml minutes^{-1} (System 2). The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

Hydrophobic frits refers to filtration tubes sold by Whatman.

SPE (solid phase extraction) refers to the use of cartidges sold by International Sorbent Technology Ltd.

Claims

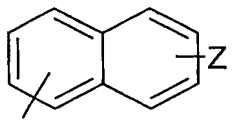
1. A compound of formula (I):

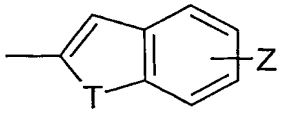


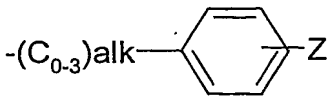
(I)

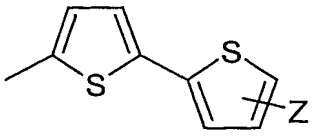
wherein:

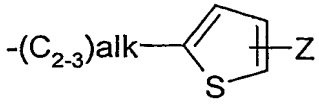
R^1 represents a group selected from:











each ring of which optionally contains a further heteroatom N,
Z represents an optional substituent halogen,
alk represents alkylene or alkenylene,
T represents S, O or NH;

R^2 represents hydrogen, $-C_{1-6}$alkyl, $-C_{1-3}$alkyl$CONR^aR^b$, $-C_{1-3}$alkylCO_2C_{1-4}alkyl, $-CO_2C_{1-4}$alkyl or $-C_{1-3}$alkylCO_2H;

R^a and R^b independently represent hydrogen, $-C_{1-6}$alkyl, or together with the N atom to which they are bonded form a 5-, 6- or 7- membered non-aromatic heterocyclic ring

optionally containing an additional heteroatom selected from O, N or S, optionally substituted by C_{1-4}alkyl, and optionally the S heteroatom is substituted by O, i.e. represents $S(O)_n$;

X represents phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-2 groups selected from: halogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -CN, -CF_3, -NR^aR^b, -C_{0-4}alkylOR^e, -$C(O)R^f$ and -$C(O)NR^aR^b$;

R^e represents hydrogen or -C_{1-6}alkyl;

R^f represents -C_{1-6}alkyl;

Y represents a group $-C(R^x)(R^z)C_{0-2}alkylNR^cR^d$;

R^x represents C_{1-4}alkyl optionally substituted by halogen;

R^z represents hydrogen or C_{1-4}alkyl optionally substituted by halogen;

R^c and R^d independently represent hydrogen, -C_{1-6}alkyl, -C_{1-4}alkylOH, or together with the N atom to which they are bonded form a 5- or 6- membered non-aromatic heterocyclic ring optionally containing an additional heteroatom selected from O, N or S, optionally substituted by C_{1-4}alkyl;
and pharmaceutically acceptable derivatives thereof.

2. A compound according to claim 1 for use in therapy.

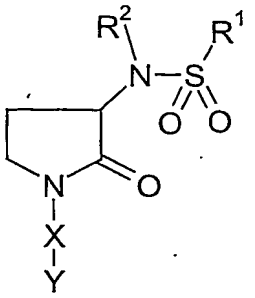
3. A pharmaceutical composition comprising a compound according to claim 1 together with a pharmaceutical carrier and/or excipient.

4. Use of a compound according to claim 1 for the manufacture of a medicament for the treatment of a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor.

5. A method of treating a patient suffering from a condition susceptible to amelioration by a Factor Xa inhibitor comprising administering a therapeutically effective amount of a compound according to claim 1.

ABSTRACT

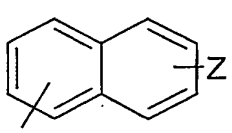
The invention relates to compounds of formula (I):

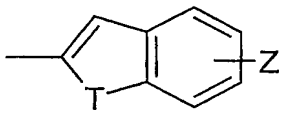


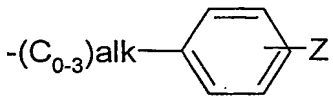
(I)

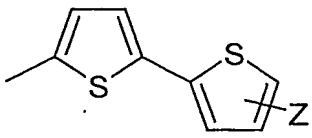
wherein:

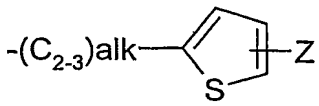
R^1 represents a group selected from:











each ring of which optionally contains a further heteroatom N,
Z represents an optional substituent halogen,
alk represents alkylene or alkenylene,
T represents S, O or NH;

R^2 represents hydrogen, $-C_{1-6}$alkyl, $-C_{1-3}$alkylCONR^{a}R^b, $-C_{1-3}$alkylCO_2C_{1-4}alkyl, $-CO_2C_{1-4}$alkyl or $-C_{1-3}$alkylCO_2H;

R^a and R^b independently represent hydrogen, $-C_{1-6}$alkyl, or together with the N atom to which they are bonded form a 5-, 6- or 7- membered non-aromatic heterocyclic ring

optionally containing an additional heteroatom selected from O, N or S, optionally substituted by C_{1-4}alkyl, and optionally the S heteroatom is substituted by O, i.e. represents $S(O)_n$;

X represents phenyl or a 5- or 6- membered aromatic heterocyclic group containing at least one heteroatom selected from O, N or S, each of which is optionally substituted by 0-2 groups selected from: halogen, -C_{1-4}alkyl, -C_{2-4}alkenyl, -CN, -CF_3, -NR^aR^b, -C_{0-4}alkylOR^e, -$C(O)R^f$ and -$C(O)NR^aR^b$;

R^e represents hydrogen or -C_{1-6}alkyl;

R^f represents -C_{1-6}alkyl;

Y represents a group $-C(R^x)(R^z)C_{0-2}alkylNR^cR^d$;

R^x represents C_{1-4}alkyl optionally substituted by halogen (e.g. CF_3, $-CH_2CF_3$);
R^z represents hydrogen or C_{1-4}alkyl optionally substituted by halogen (e.g. CF_3, $-CH_2CF_3$);

R^c and R^d independently represent hydrogen, -C_{1-6}alkyl, -C_{1-4}alkylOH, or together with the N atom to which they are bonded form a 5- or 6- membered non-aromatic heterocyclic ring optionally containing an additional heteroatom selected from O, N or S, optionally substituted by C_{1-4}alkyl;
and pharmaceutically acceptable derivatives thereof. The invention also relates to processes for the preparation of compounds of formula (I), pharmaceutical compositions containing compounds of formula (I) and to the use of compounds of formula (I) in medicine, particularly in the amelioration of a clinical condition for which a Factor Xa inhibitor is indicated.